ARTICLE

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Impact of moderate to vigorous physical activity on systemic vascular resistance in Danish adults with recently diagnosed type 2 diabetes: a cross-sectional study

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Strenuous physical activity alleviates the risk of elevated blood pressure (BP) presumably through a reduction in systemic vascular resistance (SVR). Using logistic multivariate regression models, we investigated whether moderate to vigorous physical activity (MVPA) was negatively associated with high SVR among adults with Type 2 Diabetes (T2DM). Additionally, we assessed associations between other cardiometabolic risk factors and SVR. SVR was assessed using thoracic electrical bioimpedance; high SVR was defined as ≥20% above normal. Time spent on MVPA was calculated using accelerometer data and age-specific cut points. In fasting blood samples, we measured plasma glucose and c-peptide and used the Homeostasis Model Assessment 2-Insulin Resistance (HOMA2-IR) to estimate Insulin resistance. Results are adjusted for age, sex, BP, body mass index (BMI), HOMA2-IR, medication, and smoking. We included 824 adults (mean age = 61.6 years) with recently diagnosed T2DM (interquartile range for diabetes duration = 4.9 years). 41% were females. Median MVPA was 10.7 min/day, and 50.5% had high SVR. Increments of 14.4 min/day in MVPA were independently associated with a lower risk of high SVR (OR = 0.69, [0.57;0.83]). Other risk determinants of high SVR were female sex (OR = 2.06, [1.49;2.86]), each increase in BMI of 6.16 kg/m^2 (OR = 2.20, [1.76;2.73]), and HOMA2-IR of 1.79 (OR = 2.33, [1.09;4.96]). BMI had a notably greater impact on explained variability of SVR than MVPA when comparing the coefficient of determination (pseudo-R^2, 35.0% vs. 7.9%). Although increased levels of MVPA are associated with a reduced risk of high SVR, BMI appears to have a more pronounced effect on SVR.

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INTRODUCTION

Hypertension is a common condition that affects more than 1 billion individuals worldwide and presents itself as a strong predictor for stroke and ischemic heart diseases if left untreated [1]. Arterial blood pressure is a measurable end-product of an intricate cascade of factors and is primarily mediated by a balance of cardiac output and systemic vascular resistance (SVR). Established hypertension has been suggested to be characterized by a normalized cardiac output reflecting a decrease in stroke volume, and high SVR due to vascular remodelling [2]. In parallel, high SVR has in one study been shown to be closer associated with cardiovascular events and mortality than hypertension alone [3]. In individuals with type 2 diabetes mellitus (T2DM) hypertension is up to twice as prevalent as in individuals without T2DM [4]. The coexistence of T2DM and hypertension is possibly due to the many similar risk factors, such as a sedentary lifestyle in conjunction with obesity, dyslipidemia, and elevated insulin resistance [5]. Regular physical activity promotes a long-term reduction in resting blood pressure and is well established as beneficial for cardiovascular health [6]. The blood pressure lowering effect of physical activity is well studied and pre-exist as a valid treatment option either as an isolated or additive treatment for hypertension [7]. The reduction in blood pressure through physical activity is suggested to be driven predominantly by a reduction in SVR [8]. Furthermore, active healthy individuals as opposed to those not habitually engaged in regular moderate to high intensity aerobic exercise exhibit lower resting SVR [9].

However, physical activity-based intervention studies with adults with impaired glucose tolerance or T2DM show conflicting results regarding the impact on SVR [10–12]. Overall, these findings suggest that exercise intensity and/or volume must be sufficiently high to elicit an effect on SVR in T2DM. Yet, the relative extent to which everyday physical activity, varying from moderate to vigorous intensities, is associated with SVR and how this association is modified by risk factors in T2DM remains unknown.

Therefore, the primary objective of this cross-sectional study was to determine if less time spent on moderate to vigorous physical activity (MVPA) was independently associated with high SVR among adults recently diagnosed with T2DM. Secondly, our objective was to assess if cardiometabolic risk factors and antidiabetic/antihypertensive treatment were associated with SVR and if these factors modified the association between MVPA and SVR. Third, we wanted to describe the relative contribution of low MVPA to high SVR compared to other potential confounders and mediators.

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MATERIAL AND METHODS

Population and sampling

Data for this cross-sectional study was derived from baseline data from the prospective controlled intervention study: The specialist supervised individualised multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA) [13]. The study population in IDA consisted of individuals with recent-onset T2DM recruited from the nationwide cohort of the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) [14], all treated by their general practitioner. Study participants were included, if they (1) did not have characteristics of type 1 diabetes (age < 30 years at DD2 enrolment, fasting C-peptide <300 pmol/L and GAD65-ab > 20 IU/mL), (2) had life expectancy above 2 years and (3) did not participate in other clinical trials. The median time between enrollment in DD2 and IDA was 3.6 years.

Written informed consent for IDA was obtained from a total of 1 172 eligible participants and baseline data was collected in 2013–2018 as summarized in Fig. 1.

Systemic vascular resistance

As part of the baseline examination in IDA, non-invasive impedance cardiography was recorded using the HOTMAN system (Hemo Sapiens Inc. Sedona, Arizona, USA). This allowed us to measure hemodynamic imbalances using thoracic electrical bioimpedance and provide estimates of SVR in percent of predicted normal as the primary outcome. The estimates have been validated against measurements from conventional thermodilution [15] and has previously been used to guide antihypertensive treatment [16]. Recordings from the HOTMAN system were designed to be used clinically and report SVR as a percentage deviation from predicted normal (0%). Values ≥ 20% above normal were defined as high SVR, while values < 20% were considered normal. By default, measurements of SVR were therefore obtained as a binary variable. A total of 1103 (94%) participants had complete and valid bioimpedance readings at baseline (Fig. 1).

Physical activity

At the IDA baseline visit, two weatherproof tri-axial accelerometers (Axivity AX3, Axivity, Newcastle, UK) were attached to each participants' lower back and right thigh to capture (1) physical activity volume and intensity and (2) step count and movement behaviors using the acceleration signal and thigh inclination, respectively. ActiGraph counts were generated from raw acceleration using an epoch length of 10 s. Age-specific cut points for MVPA were determined using a protocol consistent with the method described previously, which combines preferred walking speed and treadmill running at 60% VO_2max, calibrated via indirect calorimetry [17]. Time spent on MVPA was initially measured in seconds per day but aggregated to minutes per day. Likewise, sedentary time was defined as registrations below 100 counts/min [18]. Both accelerometers were worn continuously for 10 days, also during showering or other water activities. For descriptive statistics, participants were categorized based on whether they met the Danish national guidelines for physical activity, which recommend a minimum of 30 min of MVPA daily [19]. A total of 829 (75%) of the 1103 participants with bioimpedance data had valid and comprehensive accelerometer data (Fig. 1).

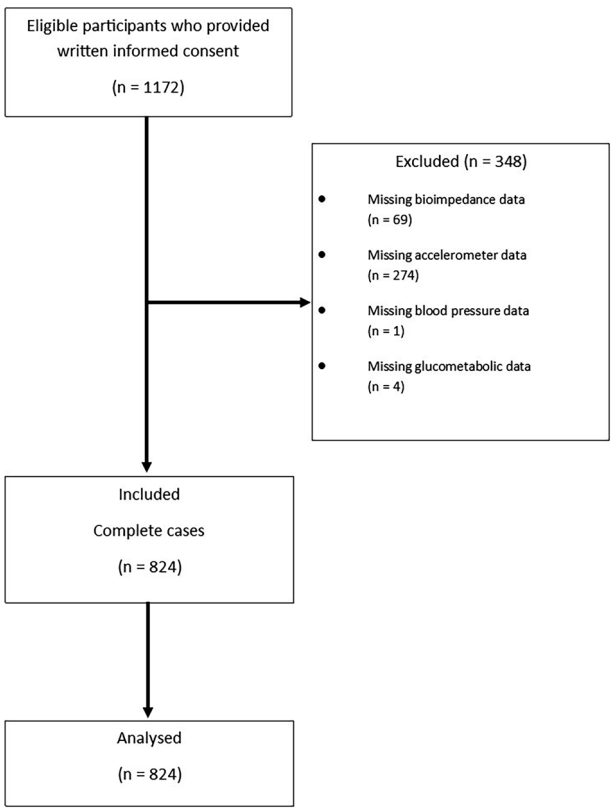

Fig. 1 Inclusion flowchart.

Confounders and mediators

At the IDA baseline visit, a medical interview was performed, where medical history and drug use were recorded. The interviews were aided by data from the participant's electronic journal and electronic drug record (Fælles Medicin Kort). Antidiabetic treatment was categorized as (a) drug naïve, (b) oral antidiabetic drugs only, (c) insulin (with or without oral antidiabetic drugs) (d) each specific antidiabetic agent and insulin type. Antihypertensive treatment was categorized in three independent ways: (a) The presence or absence of pharmaceutical treatment. (b) The total number of different antihypertensive drug types. (c) Treatments based on (1) renin-angiotensin system (RAS) blockage: Renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, (2) diuretics: Aldosterone receptor antagonists, amiloride, thiazide, loop diuretics and (3) calcium channel blockers (CCB).

A physical examination was performed including measurements of body weight and body height as well as systolic and diastolic blood pressure assessed by an automated blood pressure measurement in the seated position over 30 min at 3 min intervals using an oscillometric Mobil-O-Graph device (IEM GmbH, Aachen, Germany). Mean arterial pressure (MAP) was calculated using these readings and the following formula:

$$MAP = DBP + 1/3(SBP - DBP)$$

Where DBP is diastolic blood pressure and SBP is systolic blood pressure [20].

The usage of tobacco was self-reported and smoking status was categorized as (a) never smoked or former smoker and (b) current smoker, while the latter includes occasional smoking. In addition, measurements of HbA1c and serum creatinine were obtained from clinical measurements closest to the IDA baseline visit. The median time from laboratory measurement to the baseline visit was 54 days (IQR: 17–116) for serum creatinine and 39 days (IQR: 11–70) for HbA1c. Estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula based on age, sex, and serum creatinine [21]. The study participants' age and sex were determined by their civil registration number (CPR-number). Fasting plasma glucose and fasting serum C-peptide were obtained from the DD2 blood sample. Based on these measurements, beta-cell function (HOMA2-beta) and insulin resistance (HOMA2-IR) were estimated using the Homeostasis Model Assessment 2 (HOMA2) [22]. Lastly, LDL (low-density lipoprotein), previous cardiovascular disease (CVD) events and statin usage were also extracted from the sources described above.

Statistics

The study participants' clinical characteristics are presented based on levels of MVPA, categorized as below and at or above 30 min daily, in Table 1. For comparing the differences between the groups, we used a χ^2-test for categorical variables and a Kruskal-Wallis test for continuous variables. For the subsequent analyses, continuous values for time spent on MVPA were used.

Given the binary nature of the outcome variable, we used binary logistic regression, which allowed us to assess the association between MVPA-time and SVR as odds ratios (ORs) while adjusting for potential confounders. To determine if MVPA-time was independently associated with SVR we assessed the association in all participants in a univariate and an adjusted model. In the adjusted model we adjusted for age, sex, MAP, BMI, HOMA2-IR, usage of antidiabetic drugs, RAS blockers, diuretics, CCB, and smoking. Interaction analyses using the same adjusted model were conducted to explore potential effect modifications across the different subgroups. The subgroups

Table 1. Descriptive baseline characteristics stratified by MVPA-time (Moderate to Vigorous Physical Activity) of 824 adults recently diagnosed with type 2 diabetes from the IDA-study.

	Low MVPA <30 min/day	High MVPA >= 30 min/day	Total	*P* Value
n (%)	713 (86.5)	111 (13.5)	824 (100.0)	
High SVR, n (%)	387 (54.3)	29 (26.1)	416 (50.5)	**<0.001**
Age, years	62.0 (15.0)	59.9 (15.2)	61.6 (14.9)	**0.03**
Females, n (%)	301 (42.2)	38 (34.2)	339 (41.1)	0.11
Current smoker, n (%)	145 (20.3)	10 (9.0)	155 (18.8)	**<0.001**
Diabetes duration, years	3.6 (4.8)	3.0 (5.0)	3.6 (4.9)	0.45
BMI, kg/m^2	31.5 (7.2)	28.1 (5.8)	31.0 (7.2)	**<0.001**
Systolic BP, mmHg	128.0 (16.0)	126.0 (16.0)	128.0 (16.0)	**0.05**
Diastolic BP, mmHg	81.0 (13.0)	82.0 (12.0)	81.0 (13.0)	0.83
MAP, mmHg	97.0 (12.7)	96.3 (12.7)	96.7 (12.7)	0.51
eGFR, mL/min/1.732	88.0 (22.7)	91.1 (17.4)	88.6 (21.9)	0.13
HbA1c, mmol/mol	49.0 (10.0)	49.0 (9.0)	49.0 (10.0)	0.87
Fasting glucose, mmol/L	7.6 (2.1)	7.4 (2.0)	7.6 (2.1)	0.25
Fasting C-peptide, pmol/L	1177.0 (651.5)	989.7 (560.8)	1139.5 (652.6)	**<0.001**
HOMA2-beta, %	85.9 (49.9)	76.3 (44.5)	84.7 (49.4)	**0.01**
HOMA2-IR	3.0 (1.7)	2.4 (1.5)	2.9 (1.7)	**<0.001**
Antidiabetic treatment, n (%)				
None	75 (10.5)	14 (12.6)	89 (10.8)	
OAD	603 (84.6)	94 (84.7)	697 (84.6)	
Insulin +- OAD	35 (4.9)	3 (2.7)	38 (4.6)	0.50
Antihypertensive treatment, n (%)	527 (73.9)	70 (63.1)	597 (72.5)	**0.02**
Total # of antihypertensive drugs, n (%)				
None	186 (26.1)	41 (36.9)	227 (27.5)	
1–2	360 (50.5)	56 (50.5)	416 (50.5)	
3+	167 (23.4)	14 (12.6)	181 (22.0)	**0.01**
RAS blockade, n (%)	425 (59.6)	59 (53.2)	484 (58.7)	0.20
ARA, Amiloride, Thiazide diuretics, Loop diuretics, n (%)	290 (40.7)	30 (27.0)	320 (38.8)	**0.01**
CCB (Yes), n (%)	192 (26.9)	20 (18.0)	212 (25.7)	**0.05**
Sedentary time, min/day	610.9 (130.1)	572.6 (131.3)	605.1 (129.0)	**<0.001**
MVPA time, min/day	9.1 (11.9)	39.4 (14.5)	10.7 (15.2)	**<0.001**
Any CVD-event, n (%)	131 (18.4)	12 (10.8)	143 (17.4)	**0.05**
Statin, n (%)	516 (72.4)	72 (64.9)	588 (71.4)	0.10
LDL, mmol/L	2.1 (1.0)	2.1 (1.2)	2.1 (1.1)	0.68
Metformin, n (%)	613 (86.0)	90 (81.1)	703 (85.3)	0.18
GLP-1, n (%)	46 (6.5)	4 (3.6)	50 (6.1)	0.24
DPP4, n (%)	68 (9.5)	14 (12.6)	82 (10.0)	0.31
SU, n (%)	32 (4.5)	1 (0.9)	33 (4.0)	0.07
SGLT2, n (%)	38 (5.3)	5 (4.5)	43 (5.2)	0.72
Basal insulin, n (%)	33 (4.6)	3 (2.7)	36 (4.4)	0.36
Prandial insulin, n (%)	1 (0.1)	1 (0.9)	2 (0.2)	0.13

Values are presented in medians and interquartile ranges or numbers and column %. *P* values < 0.05 are in **bold**.
IDA The Specialist Supervised Individualized Multifactorial Treatment of New Clinically Diagnosed Type 2 Diabetes in General Practice, *SVR* systemic vascular resistance, *BMI* body mass index, *BP* blood pressure, *MAP* mean arterial pressure, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *HOMA2-beta* estimated beta cell function, *HOMA2-IR* estimated insulin resistance, *OAD* oral antidiabetic drugs, *RAS* renin-angiotensin system, *ARA* aldosterone receptor antagonist, *CCB* calcium channel blocker, *CVD* cardiovascular disease, *LDL* low-density lipoprotein, *GLP-1* glucagon-like peptide-1, *DPP4* dipeptidyl peptidase-4, *SU* sulfonylurea.

were based on selected clinical characteristics. For continuous variables, we divided the subgroups into those below and those at or above the median. *P* values for interaction were also calculated between standardized MVPA and subgroup variables. We standardized MVPA by subtracting with its mean and dividing by the standard deviation to obtain clinically relevant and applicable ORs. Additionally, when adjusting for confounders, we dichotomized antidiabetic treatment, usage of RAAS blockers, diuretics, CCB and smoking into yes/no groups.

Similarly, we computed standardized ORs for HOMA2-IR, BMI, MAP, and age to construct a comprehensive model for predicting high SVR taking

into account smoking status, dichotomized use of antihypertensive and antidiabetic medications. In this model, we executed mutual adjustments for each predictor, and standardized OR were derived for all incorporated variables.

To assess the individual impact of each variable on the model's performance, we calculated the change in various model performance metrics (pseudo R^2, Bayesian Information Criterion, and Akaike Information Criterion) when introducing each variable as the last addition to the model. Pseudo R^2 was used to assess the proportion of variability in SVR explained by each independent variable with higher values indicating a better model fit. Similarly, Akaike (AIC) and Bayesian Information Criterion (BIC) were utilized to assess the balance between model fit and complexity, penalizing overly complex models with lower values indicating a better tradeoff between complexity and model fit. Furthermore, the significance of model improvement was evaluated through a Likelihood-ratio test (LR test) after incorporating each variable into the full model.

Regarding the assumptions for binary logistic regression: The dataset was examined and there were no signs of repetitions or clustering, which could violate the assumption for independence. Multicollinearity was assessed using variance inflation factor (VIF). All included covariates had VIF values ranging from 1.01–1.37 with mean VIF 1.14, indicating no concerning multicollinearity. Furthermore, scatterplots for each predictor value and log-odds of the outcome were created to visually verify the linearity assumption. The threshold for statistical significance was set as $p < 0.05$. All statistical analyses were performed using Stata BE version 18 (StataCorp LLC, College Station, TX, US).

Post-hoc analyses

To further explore potential interactions between MVPA and SVR in relation to sex and age, we conducted post-hoc analyses. These included both crude and adjusted logistic regression models while stratifying by sex and age groups (<50 and >50 years old), using the same data transformations and covariates as described in the main model above. The age cutoff was chosen to differentiate between pre- and postmenopausal women, though it was not based on specific clinical criteria.

RESULTS

In this study, following a complete case principle for exposure and outcome variables, of the total 1 172 study participants, 824 (70%) had complete and valid data sets. The study participants' characteristics stratified by levels of MVPA are presented in Table 1.

Baseline characteristics

Participants who engaged in 30 min or more MVPA daily compared to those engaging in less than 30 min MVPA daily had significantly lower prevalence of high SVR ($p < 0.001$), were younger ($p = 0.03$), had a lower proportion of current smokers ($p < 0.001$), had lower BMI ($p < 0.001$), lower SBP ($p = 0.05$), lower fasting C-peptide ($p < 0.001$), lower HOMA2-beta ($p = 0.01$), and a lower HOMA2-IR ($p < 0.001$) (Table 1). Furthermore, they were less likely to be on antihypertensive treatment ($p = 0.02$), less likely to use more than two different antihypertensive drugs ($p = 0.01$), had a lower diuretics usage ($p < 0.001$), and lower calcium channel blocker usage ($p = 0.03$). No significant differences in antidiabetic treatment were observed between the groups in each category. Finally, participants engaging in 30 min or more MVPA daily had less sedentary time daily compared to those engaging in less than 30 min ($p < 0.001$), had fewer previous CVD events ($p = 0.05$), while no differences in LDL levels were observed.

Association between moderate to vigorous physical activity and systemic vascular resistance

Details of the overall and subgroup adjusted analyses of the association between standardized MVPA and dichotomized SVR are shown in Fig. 2. Results from univariate analyses are shown in Supplementary Table 1. An increase of 1 SD in MVPA (14.4 min/day) was associated with a lower risk of having high SVR (OR = 0.57 [0.48;0.58]) in crude analysis. This inverse association was only slightly attenuated in the full model (OR = 0.69 [0.57;0.83]) when adjusting for age, sex, MAP, medication, HOMA2-IR, smoking and BMI. The association between MVPA and SVR was not modified by age, sex or any of the other clinical variables with non-significant p-values for all interactions in crude ($p > 0.19$) and adjusted analyses ($p > 0.249$).

Predictors of high systemic vascular resistance

Results from crude and adjusted ORs of the association between the selected predictors and dichotomized SVR are shown in Table 2. As we standardized the continuous variables, an increase of 1 SD corresponds to an increase in 1.79 in HOMA2-IR, 6.16 kg/m^2 in BMI, 9.9 mmHg in MAP and in 10.6 years in age.

In our full model, we found that female sex (OR = 2.06 [1.49;2.86]), higher levels of HOMA2-IR (OR = 2.33 [1.09;4.96]), BMI (OR = 2.20 [1.76;2.73]), MAP (OR = 1.67 [1.39;2.00]) and antidiabetic drug usage (OR = 1.70 [1.01;2.87]) were positively and independently associated with high SVR (Table 2). Conversely, MVPA was the only factor negatively associated with high SVR (OR = 0.69 [0.57;0.83]). In the fully adjusted model neither age, antihypertensive drug use, nor smoking status were significantly associated with high SVR.

The relative impact of each variable on the model performance when added last in the full model is depicted in Fig. 3. For reference, in our analysis we calculated pseudo R^2 to 0.1925, meaning that the full model explains 19.3% of the variability of having high SVR (Table 2). Age (0.52%, $p = 0.276$), smoking status (1.53%, $p = 0.065$) usage of antihypertensive (0.79%, $p = 0.186$) and antidiabetic drugs (1.85%, $p = 0.043$) contributed minimally to pseudo R^2. MVPA (7.90%, $p = 0.0001$), sex (9.38%, $p < 0.0001$) and MAP (17.45%, $p < 0.0001$) shared similar results of a moderate increase, while BMI (35.0%, $p < 0.0001$) contributed the most to model performance. The contributions to model performance of all variables except smoking status, antihypertensive drug use and age were significant when evaluated by Likelihood-Ratio test.

Post-hoc

Results from crude and adjusted ORs of the association between standardized MVPA and dichotomized SVR while stratifying by sex and specified age groups are presented in Supplementary Table 2.

In females aged >50 years, an increase of 1 SD in MVPA was associated with a lower risk of having high SVR (OR = 0.58 [0.43;0.77]) in crude analysis, and the association remained significant, though attenuated, in the adjusted analysis (OR = 0.71[0.51;0.99]).A similar pattern was observed in males aged >50 years in crude (OR = 0.55[0.43;0.71]) and adjusted analysis (OR = 0.67[0.51;0.89]).In contrast, no significant associations between MVPA and SVR were found in either sex in the <50 years age group. Interaction terms between MVPA and sex in the specified age groups were non-significant in both crude and adjusted models (all p-values > 0.281), suggesting no evidence of statistically significant effect modification.

DISCUSSION

In this cross-sectional study, we explored possible associations between everyday physical activity measured as time spent on MVPA and SVR among Danish adults recently diagnosed with T2DM. Furthermore, we assessed associations between selected risk factors and SVR. This study has three main findings: (1) Increased MVPA was associated with a lower risk of having high SVR independent of other clinical characteristics and without any effect modification (2) Overall, the five main factors associated with high SVR were higher BMI, higher mean arterial blood pressure, female sex, less time spent on MVPA, and more insulin resistance (3) BMI had a notably greater impact on explained variability of SVR than MVPA.

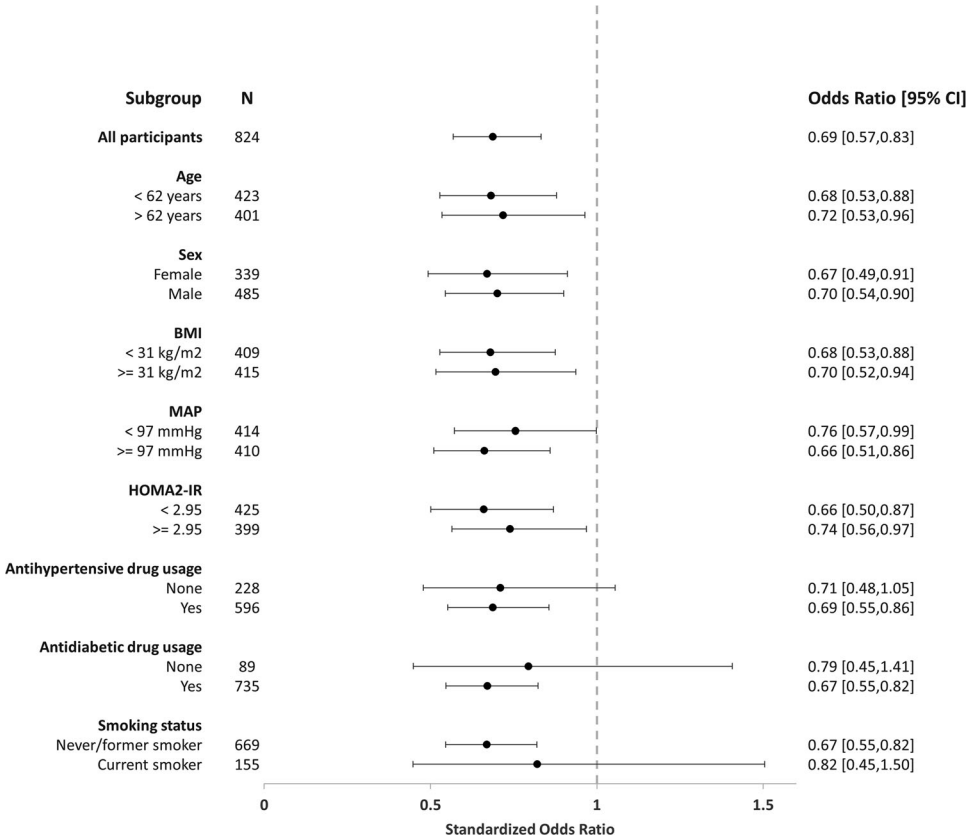

Fig. 2 Forest plot of adjusted odds ratios from overall and subgroup analyses on the association between standardized MVPA (Moderate to Vigorous Physical Activity) and SVR (Systemic Vascular Resistance): adjusted odds ratios were obtained from binary logistic regression assessing the association between standardized MVPA-time and dichotomized SVR as normal or high SVR. MVPA was standardized by subtracting with its mean and dividing by the standard deviation. An increase in 1 SD in MVPA corresponds to an increase of 14.4 min/day. The dashed line intercepts odds ratio = 1. In the adjusted model we adjusted for age, sex, MAP, usage of antidiabetic and antihypertensive drugs, HOMA2-IR, smoking and BMI. Subgroups based on continuous variables were divided into those below and at or above the median. *P*-values for interaction terms were all > 0.249 and therefore not significant. BMI body mass index, MAP mean arterial pressure, HOMA2-IR estimated insulin resistance.

Table 2. Evaluation of the standardized logistic model associations between selected clinical characteristics and SVR (Systemic Vascular Resistance).

Crude				Adjusted						
Predictor	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**Δ-% R^2**	**Δ-% AIC**	**Δ-% BIC**	***P* Value (LR test)**
BMI	2.81	[0.48;0.68]	**<0.001**	2.20	[1.76;2.73]	**<0.001**	34.99	−5.52	−4.84	**<0.0001**
MAP	1.57	[4.55;19.58]	**<0.001**	1.67	[1.39;2.00]	**<0.001**	17.45	−3.16	−2.56	**<0.0001**
Female sex	1.79	[1.35;2.38]	**<0.001**	2.06	[1.49;2.86]	**<0.001**	9.38	−1.76	−1.22	**<0.0001**
MVPA	0.57	[1.35;1.83]	**<0.001**	0.69	[0.57;0.83]	**<0.001**	7.90	−1.47	−0.94	**0.0001**
HOMA2-IR	9.44	[0.72;0.94]	**<0.001**	2.33	[1.09;4.96]	**0.029**	2.39	−0.34	0.16	**0.0229**
Antidiabetic drug use, yes/no	1.95	[1.12;2.06]	**0.004**	1.70	[1.01;2.87]	**0.046**	1.85	−0.22	0.27	**0.043**
Smoking status, current smoker/never or former smoker	0.87	[1.23;3.08]	0.449	0.68	[0.45;1.03]	0.066	1.53	−0.15	0.34	0.0654
Antihypertensive drug use, yes/no	1.52	[0.62;1.24]	**0.008**	1.29	[0.89;1.87]	0.187	0.79	0.03	0.50	0.186
Age	0.82	[0.42;0.74]	**0.005**	0.91	[0.76;1.08]	0.276	0.52	0.09	0.56	0.276

Values were obtained using binary logistic regression of the association between the selected clinical predictors and dichotomized SVR as normal or high SVR. In the model we mutually adjusted for each predictor and continuous variables were standardized by subtracting from their mean and dividing by the standard deviation. An increase of 1 SD in MVPA corresponds to an increase of 14.4 min/day, in HOMA2-IR an increase of 1.79, in BMI an increase of 6.16 kg/m2, in MAP an increase of 9.9 mmHg and in age an increase of 10.6 years. Delta-% R^2 was calculated as the relative change in pseudo R^2 when each of the variables were added last to the full model. Pseudo $R^2 = 0.1925$, AIC = 942.31, BIC = 989.45 for the full model. *P* values < 0.05 are in **bold**.

AIC akaike information criterion, *BIC* bayesian information criterion, *LR*-test likelihood-ratio test, *MVPA* moderate to vigorous physical activity, *HOMA2-IR* estimated insulin resistance, *BMI* body mass index, *MAP* mean arterial pressure.

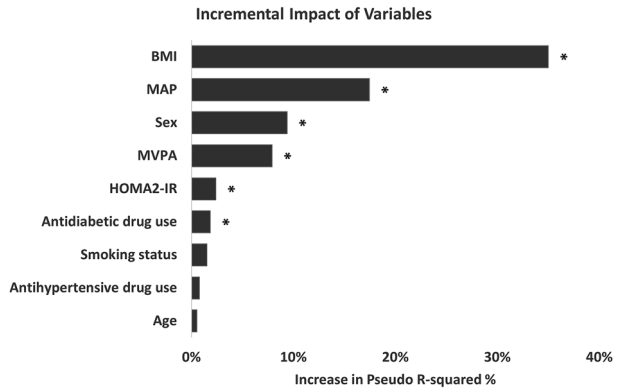

Fig. 3 Incremental impact of selected standardized variables on pseudo R-squared when added last to the model: pseudo R2 values were obtained using binary logistic regression of the association between the selected clinical predictors and dichotomized SVR as normal or high SVR. In the model we mutually adjusted for each predictor. Increase in R2 was evaluated after introducing each variable as the last addition to the model. For the full model pseudo R2 = 0.1925. * indicates a significant improvement in model performance evaluated by LR-test. MVPA moderate to vigorous physical activity, HOMA2-IR estimated insulin resistance, BMI body mass index, MAP mean arterial pressure, LR-test likelihood ratio test.

Our findings indicate that increasing levels of everyday physical activity evaluated by time spent on MVPA is associated with reduced risk of high SVR in persons with T2DM, thereby complementing studies in healthy subjects that show decreased SVR after training [9, 23]. Possible physiological explanations for the association have been proposed as improvements in production of endothelium-derived substances such as nitric oxide, and arterial restructuring mediated by the repeated hemodynamic stimulation during physical activity [24]. However, our findings contrast results from a recent study, where individuals recently diagnosed with T2DM, who underwent a 12-month 4-day endurance and strength program, did not show a significant reduction in SVR [11]. First, our study employed a cross-sectional design, limiting our ability to assess changes in SVR over time. Therefore, direct comparisons with longitudinal intervention studies should be made with caution. However, differences in study design and sample size could influence the observed outcomes. Our study focused on accelerometer-derived time spent on moderate-to-vigorous physical activity, which, by definition, includes a broad range of activities from walking briskly to running and participating in strenuous fitness classes [25]. This could be considered as "daily living" physical activity rather than strictly controlled exercise regimens often used in intervention studies, which may focus on more structured volumes and intensities of exercise. The exercise intervention in the referenced study involved four sessions per week – two days of endurance training at 65–75% VO_{2max} and two days of progressive resistance training. While the intensity of endurance training was similar to MVPA in our study, we did not monitor resistance training activity, which may influence study results. It is also possible that the biweekly endurance program in terms of exercise volume and/or intensity over 12 months was not sufficient to elicit a meaningful effect on SVR even when combined with resistance training. Another important factor is exercise adherence and compliance. Although one endurance session per week was supervised, adherence to the full program may have varied. Participant motivation, perceived barriers, and logistical challenges in attending four sessions weekly could have impacted compliance and, in turn, the intervention's effectiveness. Lastly, the authors of the referenced study concluded that exercise alone may not be sufficient to reverse unfavorable vascular changes related to SVR in T2DM. This further suggests that an isolated increase in MVPA may not independently affect SVR, emphasizing the complexity of vascular remodeling and the potential need for multifactorial approaches.

We found BMI, MAP, HOMA-IR and sex to be associated with SVR; these factors are intrinsically intertwined with MVPA. We have measurements of current MVPA, however, the accumulated effect of low lifetime MVPA probably contributes to these factors also. Obesity is considered as a key determinant in the development of hypertension. Especially visceral adipose tissue poses as a probable culprit for increasing sympathetic nervous system activity, and therefore SVR, through elevated circulating catecholamine concentrations [26]. In a previously mentioned study, BMI together with physical activity was also shown to independently predict adulthood SVR, highlighting the significance of early weight management [23]. In addition, obesity is closely linked to insulin resistance, as long-term overnutrition leads to ectopic fat deposition in organs throughout the body, which in turn stimulates a pro-inflammatory response systemically leading to insulin resistance [27]. Insulin resistance affects endothelial cells, impairing their ability to produce and release nitric oxide, a vasodilator, which may weaken arterial dilatation and increase SVR [28]. Moreover, insulin resistance can stimulate the sympathetic nervous system causing increased release of norepinephrine thereby increasing SVR [29]. In addition, in individuals with metabolic syndrome, which is characterized partly by abdominal obesity, SVR is higher at rest [30]. To summarize, this suggests that obesity and insulin resistance are closely related in the context of SVR, and our findings related to BMI and HOMA2-IR are also consistent with findings from other studies.

We found that female sex was associated with high SVR, while male sex was associated with a lower OR of high SVR. One possible explanation for this could be that because males have higher prevalence of hypertension, they will be more intensively treated which potentially could attenuate the association between male sex and SVR. In turn, high BMI could be the driving factor between female sex and SVR. The current literature on the association of sex and SVR is ambiguous some with similar SVR indices between sexes [31] and other with higher SVR in women than in men [32]. A decline in androgen levels as seen during menopause may lead to endothelial dysfunction and consequently increased vascular resistance [33]. Another possible explanation may be that there is an interaction between sex and age in the context of SVR, meaning that blood pressure is regulated through SVR differently between sexes in different age groups. A study has suggested that while a direct relationship between muscle sympathetic tone and SVR exists in young men, in young women this relationship is not seen [34]. The study further explains that with advancing age, the relationship between muscle sympathetic tone, SVR and blood pressure also varies between men and women, suggesting a sex *and* age dependent regulation of blood pressure through SVR [34]. To expand on our findings, we conducted stratified post-hoc analyses to examine the significance of sex and age in modulating SVR through MVPA. Increased levels of MVPA were associated with a reduced risk of high SVR in both sexes among participants aged >50 years. However, this association was not statistically significant in participants aged <50, regardless of sex. These results suggest that while the association between MVPA and SVR is consistent across sex, it may be influenced by age. More likely, the lack of significant associations in the younger age group reflects an insufficient sample size for both sexes and conclusions should be drawn with caution. Although we did not find statistical evidence of sex *and* age effect modification, our findings highlight the need for further research with larger and more balanced sample sizes across sex and age groups.

This study is observational and therefore can only identify associations and not conclude causality. Nonetheless, in this study, we obtained effect sizes from our adjusted analyses, while minimizing the risk for potential confounders that could interfere with the associations between SVR and the investigated variables. The study's strengths include the large sample size of persons with recently diagnosed T2DM from a nationwide cohort.

Registration of physical activity was objectively performed using accelerometers as opposed to self-reported questionnaires. Accelerometers offer a more accurate assessment of daily activity exposure by providing objective and quantitative measurements of both duration and intensity, thereby eliminating potential biases associated with patient recall [35]. However, a major limitation in our study was the lack of continuous measurements for SVR. Having a continuous spectrum to analyze could have provided increased statistical power through preservation of information and most importantly, it could have allowed us to explore dose-response relationships between absolute units of SVR and the investigated predictors in-depth. In addition, it is uncertain whether the study participants, willingly or unwillingly, changed in their physical activity level during the 10 days of physical activity registration. Although unlikely, it could represent a potential limitation to the accuracy of the data on MVPA and association to SVR. We also used BMI as the sole measure of adiposity and lacked more specific measures such as waist circumference or imaging-based assessment of visceral fat, which may have provided further insight into the link between adiposity and SVR. Additionally, more detailed information on hormonal status, including hormonal biomarkers, menopausal state, and hormonal replacement therapy, would be valuable in investigating the significance of sex in modulating SVR. Lastly, the pseudo-R^2 value of 0.193 indicates that the model explains approximately 19% of the variability in SVR. While this is reasonable in the context of a complex, multifactorial outcome, it underscores that other unmeasured biological, behavioral, or genetic factors likely contribute to SVR. For example, while we included HOMA2-IR as a marker of insulin resistance, we did not have data on inflammatory markers (e.g., CRP, IL-6), which could have provided further insight into the mechanisms linking adiposity and SVR.

In summary, our study found that less daily time spent on MVPA was independently associated with an increased risk of high SVR among adults recently diagnosed with T2DM. Other main determinants of high SVR were higher BMI, female sex, and increased insulin resistance. Our results indicate that although increased time spent on MVPA is advantageous for reducing risk of high SVR, BMI appears to have a more pronounced effect. Clinically, this would suggest weight loss as the most important factor in attenuating SVR, which in turn is closely related to hypertension. Increasing the level of everyday physical activity could serve a dual purpose in managing both SVR and promoting weight loss in T2DM. Future research should focus on validating our findings and explore potential impact of changing time spent on MVPA on SVR to identify therapeutic targets for time spent on MVPA in relation to SVR.

SUMMARY

What is known

- Physical activity reduces blood pressure presumably through a reduction in systemic vascular resistance.
- In non-diabetic populations, habitually physically active individuals engaging in moderate to high intensity aerobic exercise exhibit a lower resting systemic vascular resistance.
- In subjects with impaired glucose tolerance or type 2 diabetes mellitus, intervention studies show conflicting results.

What this study adds

- In adults with recently diagnosed type 2 diabetes mellitus, increased time spent on everyday moderate to vigorous physical activity (MVPA) is associated with a reduced risk of having increased systemic vascular resistance.
- Although time spent on MVPA has a significant role in managing systemic vascular resistance, BMI was closer associated with SVR than MVPA.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are not publicly available due to Danish data security regulations but are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization of IDA study: JVS, TBO, JSN and Henning Beck-Nielsen Conceptualization of current study: SBN, TBO and JVS. Data curation: JVS. Formal analysis: SBN, TBO and JVS. Investigation: TBO and JVS. Methodology: SBN, TBO, JVS, SLD, SFK, JSN and MHO. Supervision: TBO and JVS. Validation: TBO, JVS, SLD, SFK, JSN and MHO. Writing – original draft preparation: SBN, TBO and JVS. Writing – review & editing: TBO, JVS, SLD, SFK, JSN and MHO. All authors provided critical comment.

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COMPETING INTERESTS

MHO has in relation to lectures received honorary from Novo Nordisk A/S, Teva A/S, and AstraZeneca A/S.

ETHICAL APPROVAL

The IDA study was approved by the Regional Committee on Medical Health Ethics (Region of Southern Denmark S-20120186), the Danish Data Protection Agency and Medicines Authority (journal no. 2012120204) and was conducted in concordance with the Helsinki declaration II.

ADDITIONAL INFORMATION

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